Revised models of endocannabinoid signaling at inhibitory synapses in the brain

Min, R.

2009

Summary

Revised models of endocannabinoid signaling at inhibitory synapses in the brain

The research described in this thesis focuses on how endocannabinoids influence the communication between brain cells. Here, I will first describe what endocannabinoids are and why it is interesting to study them. Then I will shortly explain how brain cells communicate, and how we can record this. Finally, I will shortly describe the main findings from this thesis.

Endocannabinoids are substances that naturally occur in the brain. Their name is a concatenation of the words 'endogenous' (meaning occuring within the body) and 'cannabinoid'. The second part of the name derives from the similarities between endocannabinoids and the active component from the *Cannabis sativa* plant (marijuana), Δ9-THC. The *Cannabis sativa* plant has been known for thousands of years for its psychoactive and medicinal properties. Both Δ9-THC and endocannabinoids affect the brain by activating the same target, a so-called cannabinoid receptor. This cannabinoid receptor is very abundant in the brain, which suggests that it plays an important role in normal brain functioning.

Recent studies have shown that endocannabinoids in the brain are important for learning and memory, that they play a role in the processing of pain, and that they are important for the regulation of food intake. Pharmacological intervention in endocannabinoid signaling is seen as a promising treatment for a multitude of problems like pain, nausea, obesity and depression. Furthermore, a malfunctioning endocannabinoid system seems to play a role in several neurological diseases, including schizophrenia and epilepsy. Therefore, it is important to have a better understanding of the exact way in which endocannabinoids work. I will now shortly describe how brain cells communicate, and what role endocannabinoids play in this.

The principle task of the brain is to translate sensory information that it receives from the senses into proper behavioral output. To do this, the billions of brain cells (neurons) in the brain assemble into complex neuronal networks. These neurons communicate by means of so-called synapses. A synapse is the contact point between a sending (presynaptic) neuron and a receiving (postsynaptic) neuron. When a synapse is active, the presynaptic neuron releases a substance called a neurotransmitter. This neurotransmitter activates and opens ionic channels on the postsynaptic neuron. The opening of these ionic channels permits the flow of electrically charged ions in and

out of the postsynaptic neuron, which causes an electrical current in this neuron. This current can either activate or inhibit the postsynaptic neuron (depending on the nature of the neurotransmitter and the properties of the ionic channels). Every neuron in the brain receives thousands of synapses, while also sending thousands of synapses to other neurons.

In most experiments described in this thesis we have recorded the electrical activity of synapses. To do this, we use brain slices of mice or rats. In such slices a part of the neuronal network remains intact. By contacting a neuron in this network with a tiny glass electrode, it is possible to record the electrical activity in this neuron. It is possible to simultaneously record the activity of two neurons that make a synaptic contact. By stimulating the presynaptic neuron while recording activity in the postsynaptic neuron, we can map the properties of the synapse between these neurons.

In order to properly process sensory information, it is necessary that synapses can temporarily change their strength. The property of synapses to temporarily strengthen of weaken is termed 'synaptic plasticity'. Synaptic plasticity can occur on both sides of the synapse: the presynaptic neuron can change the amount of neurotransmitter release, and the postsynaptic neuron can change the amount or properties of the receiving ionic channels. In this way a synapse can temporarily strengthen (more neurotransmitter release or a stronger response of the ionic channels) or weaken (less neurotransmitter release or a weaker response of the ionic channels).

Endocannabinoids play a role in several forms of synaptic plasticity. The classical way in which endocannabinoids work is as follows: strong activity in the postsynaptic neuron triggers the formation of endocannabinoids. These endocannabinoids subsequently travel to the presynaptic neuron, where they activate the cannabinoid receptor. Activation of this receptor causes a reduction in neurotransmitter release, resulting in a weakening of the synapse. This weakening can last for tens of seconds, until the endocannabinoids are degraded.

Until now it was assumed that an enzyme termed DAG lipase is involved in the formation of endocannabinoids in many neurons. In chapter 2 of this thesis we study a brain region which contains many cannabinoid receptors, and which is important for memory formation: the hippocampus. We study synapses in the hippocampus which show the above described form of endocannabinoid mediated synaptic plasticity. We show that blocking the activity of DAG lipase does not affect this form of synaptic plasticity. This means that, surprisingly, DAG lipase is not involved in the formation of endocannabinoids in this form of plasticity. Future research is needed to find out in which alternative way endocannabinoids are formed in this process.

In chapters 3 and 4 we describe an entirely novel way in which endocannabinoids can mediate synaptic plasticity. Until now it was thought that cannabinoids only influence synaptic transmission by activation of presynaptic cannabinoid receptors. In chapters 3 and 4 we show that endocannabinoids can also modulate synapses that lack this receptor.

Using several different approaches, we show that cannabinoids can directly change the properties of some postsynaptic ion channels. This means that synapses which lack the cannabinoid receptor can still show endocannabinoid mediated synaptic plasticity.

The research described in this thesis shows that endocannabinoids are versatile substances, which can change brain functioning not only through activation of specialized cannabinoid receptors, but also by direct modulation of unexpected targets. Hopefully, the increased understanding of these signaling processes will further our understanding of how the brain works, and enable more specific pharmacological intervention in brain diseases involving endocannabinoid signaling.